REMARKS

The specification has been amended to capitalize trademarks and remove reference to embedded hyperlinks.

Applicants have cancelled Claims 8 and 10 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 1-7 and 9 to remove reference to the Figures. Claims 1-5 have been amended to add the limitation that the claimed polypeptides are more highly expressed in normal lung tissue compared to lung tumor, or encoded a polynucleotide that is more highly expressed in normal lung tissue compared to lung tumor. Claims 1-7 and 9 have been amended to add the language "having the amino acid sequence of amino acids 34-321 of" SEQ ID NO:10. Claims 1-6, and 9 have been amended to specify the amino acids of the extracellular domains. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendment to Claims 1-5 regarding differential expression in normal lung and lung tumor can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification. Support for the amendment to Claims 1-7, and 9 regarding amino acids 34-321 can be found, for example, in paragraph [0196]. Support for the amendment to Claims 1-6, and 9 regarding the extracellular domains can be found, for example, in Figure 10.

Claims 1-7, 9, and 11-13 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed September 8, 2004. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Priority Determination

The PTO has stated that because the claimed nucleotide has no utility, the priority under 35 U.S.C. § 120 is set at the instant filing date, May 1, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, with is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/088030 filed 6/4/1998.

Applicants submit that for the reasons stated below, the claimed polypeptides have a credible, substantial, and specific utility. The sequences of SEQ ID NOs: 9 and 10 were first disclosed in US Provisional Application 60/088030 filed 6/4/1998. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Specification

The disclosure was objected to by the PTO as containing embedded hyperlinks and/or other form of browser-executable code. The specification has been amended to remove reference to embedded hyperlinks. The specification has been further amended to indicate trademarks by capitalizing the trademarks and providing generic terminology.

As an initial matter, Applicants wish to point out that amino acid 34 of SEQ ID NO: 10 is the initiator methionine, and amino acids 1-33 are not part of the PRO874 polypeptide. The full-length PRO874 polypeptide consists of amino acids 34-321 of SEQ ID NO: 10. In addition, the start codon of SEQ ID NO: 9 is the ATG beginning at nucleotide 100 of SEQ ID NO: 9. The amendments to the Claims to reflect this do not add new matter, as the specification indicates at paragraph [0196] that methionine 34 can be the starting amino acid of PRO874.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected the pending claims under 35 U.S.C. § 101 as lacking patentable utility. The PTO concedes that the cited utilities are credible. However, the PTO alleges that the invention lacks both substantial and specific utility. Applicants respectfully disagree.

Substantial Utility

The PTO rejects the asserted utilities for the polypeptide of SEQ ID NO: 10. The PTO notes that SEQ ID NO: 10 does not begin with an initiator methionine and therefore less than a full-length protein is disclosed. The PTO states that while the data of Example 18 provides only a use of a limited number of nucleic acid probes, the specification provides no information regarding the level of expression, activity, or role in cancer of PRO874. Relying on Allman *et al.* (Blood, 87(12):5257-68 (1996)), the PTO further notes that differential tissue nucleic acid expression is not always correlated with protein levels. The PTO also notes that structural similarity does not establish the function of a protein. The PTO concludes that the instant claims encompass a protein of as yet undetermined function or biological significance.

Utility need NOT be Proved to an Absolute Certainty – a Correlation between the Evidence and the Asserted Utility is Sufficient

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (emphasis in original, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal

evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change (here a decrease) in gene expression in cancer cells establishes a "significant probability" that the encoded polypeptide will also be changed (here, decreased) in cancer based on "a reasonable correlation therebetween".

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the PRO874 polypeptide is useful as a diagnostic tool for cancer.

Applicants have established that the Gene Encoding the PRO874 Polypeptide is Underexpressed in Lung Tumors compared to Normal Lung Tissue and is Useful as a Diagnostic Tool

Applicants note that the PTO has acknowledged that differential expression of the PRO874 gene reported in Example 18 provides utility for certain nucleic acid probes. However, the PTO states that the specification provides no information regarding the level of expression, activity, or role in cancer of PRO874.

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraphs 6 and 7, Mr. Grimaldi

explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). As Mr. Grimaldi states, "If a difference is detected, this indicates that *the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes*, to screen samples to differentiate between normal and tumor." (Paragraph 7, emphasis added).

The data presented in Example 18 show that the gene encoding PRO874 is more highly expressed in normal lung tissue compared to lung tumor. As the Grimaldi declaration indicates, the disclosed gene and its corresponding polypeptide and antibodies are therefore useful as diagnostic tools. No additional research into how PRO874 is related to cancer is required to use the disclosed polynucleotides, polypeptides and antibodies to distinguish tumor cells from their normal tissue counterparts. As is explained below, Applicants submit that the gene expression data reported in Example 18 are sufficient to establish a specific and substantial utility not only for nucleic acid probes, but the PRO874 polypeptide as well.

Applicants have established that the Accepted Understanding in the Art is that there is a Reasonable Correlation between Gene Expression and Expression of the Encoded Protein

Applicants next address the PTO's argument the specification provides no information regarding the level of expression, activity, or role in cancer of PRO874, and that differential tissue nucleic acid expression is not always correlated with protein levels. The PTO appears to be arguing that because there is no *necessary* correlation between gene expression and protein expression, evidence of underexpression of the gene in cancer does not provide utility for the protein.

As discussed above, evidence of utility does not have to be to an absolute certainty, and therefore there does not need to be a *necessary* connection between gene expression and protein expression. Rather, there need only be a *reasonable* correlation between the evidence offered

and the asserted utility such that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true. As detailed below, Applicants assert that it is well-established in the art that in general, the level of protein is positively correlated to the level of mRNA, and thus data indicating that a gene is over- or underexpressed in cancer is persuasive evidence that the encoded protein is over- or underexpressed in cancer.

In support of this assertion, Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 2). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (4th ed. 2002) submitted herewith as Exhibit 4). Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Molecular Biology of the Cell at 302, emphasis added. Similarly, figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Molecular Biology of the Cell at 364. This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Molecular Biology of the Cell at 379.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts from the Molecular Biology of the Cell establish that the accepted understanding in the art is that there is a correlation between gene expression and the level of the encoded protein.

As evidence to the contrary, the PTO relies on a single reference, Allman *et al.* (Blood, 87(12):5257-68 (1996)), for the conclusion that "differential tissue nucleic acid expression is not always correlated with protein levels." Office Action at 4. The PTO focuses on the finding reported by Allman *et al.* that germinal center B cells express dramatically more BCL-6 protein than resting B cells, despite similar BCL-6 mRNA levels in the two cell populations. Office Action at 7. The PTO concludes that therefore, the [higher] expression of SEQ ID NO: 9 in normal lung compared to lung tumor does not provide a readily apparent use for the PRO polypeptide.

While Applicants acknowledge that there is no *necessary* correlation between gene expression levels and protein expression levels, a *necessary* correlation is not required to establish an asserted utility. Instead, there need only be a reasonable correlation. The Allman reference actually supports Applicants' assertion that it is well-established in the art that in general, the level of protein is positively correlated to the level of mRNA.

In the discussion of their finding that mRNA and DNA levels were not correlated, Allman *et al.*refer to the discovery as a "striking dichotomy." Allman *et al.* at 5265, second column, last

paragraph. They also state that "an *unanticipated* finding was that the higher BCL-6 protein levels...could not be fully accounted for by increased mRNA expression." Allman *et al.* at 5267, column 1, carryover paragraph (emphasis added). Both of these statements indicate that normally, protein expression is correlated to mRNA levels, and their findings to the contrary were unexpected for that reason.

In light of the lack of significant support for the PTO's argument, Applicants submit that the PTO has failed to establish a reason for one of skill in the art to doubt the asserted utility. Even if it has, Applicants have offered sufficient evidence to rebut the PTO's argument and establish that there is a reasonable correlation between gene expression and protein expression. The declarations of Grimaldi and Polakis, the excerpts from the Molecular Biology of the Cell, and the statements of Allman *et al.* all support this assertion.

The PTO is reminded that absolute predictability is not required. Considering all the evidence, Applicants have established that it is more likely than not that one of skill in the art would be convinced, to a reasonable probability, that because the PRO874 mRNA is expressed at a higher level in normal lung tissue compared to lung tumor, the PRO874 polypeptide is also expressed at a higher level in normal lung tissue compared to lung tumor.

One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue has utility, for example, to generate antibodies to the protein for use as a cancer diagnostic. This utility would include any polypeptide that can be used to generate specific antibodies to PRO874 or related polypeptides that are differentially expressed in cancer compared to normal tissue. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the claimed PRO874 polypeptides as cancer diagnostic tools.

The Claimed Polypeptides would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Protein Expression

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO874, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 5, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 6), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 7). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a protein encoded by a gene that is differentially expressed in cancer would still have utility as a diagnostic tool. Thus, Applicants have demonstrated another basis of support for the utility of the claimed polypeptides.

Specific Utility

The PTO also states that the claimed invention lacks a specific utility. Applicants respectfully disagree.

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that the claimed polypeptides lack a specific utility. Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention."

M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO874 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed polypeptides.

Applicants have provided significant data which show that the gene encoding the PRO874 polypeptide is more highly expressed in normal lung tissue compared to lung tumor. It is well-established in the art that the encoded protein would have the same expression pattern. These data are therefore persuasive evidence that the PRO874 polypeptide is associated with lung tumors, and would have utility as a diagnostic tool. This is a specific utility – it is not a general utility that would apply to the broad class of polypeptides. Thus, contrary to the assertions of the PTO, Applicants submit that they have established that the asserted utility is specific to the claimed polypeptides.

Conclusion

Given the totality of the evidence provided, Applicants submit that they have established a credible, substantial, and specific utility for the claimed polypeptides as diagnostic tools. According to the M.P.E.P. and case law cited above, irrefutable proof of a claimed utility is **not** required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants have offered sufficient evidence to establish that there is a reasonable correlation between gene expression and protein expression. Applicants have established that it is more likely than not that based on the data reported in Example 18, one of skill in the art would be convinced, to a reasonable probability, that the PRO874 protein is overexpressed in certain cancers, and therefore has a credible, substantial, and specific utility as a diagnostic tool. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO has rejected Claims 1-13 as failing to comply with the enablement requirement. According to the PTO, the specification does not enable any person skilled in the art to make and/or use the invention. The PTO argues that the claims encompass an unreasonable number of inoperative polypeptides which the skilled artisan would not know how to use. The PTO states that there are no working examples of polypeptides less than 100% identical to SEQ ID NO: 10,

and that the claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation. In addition, the PTO states that predicting structure and function from primary amino acid sequence data is extremely complex. The PTO concludes that it would require undue experimentation to use the invention commensurate in scope with the claims. Applicants respectfully traverse.

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection to the extent that it is based on a lack of utility for the claimed polypeptides.

In addition, Applicants have amended the claims to incorporate the limitation that the claimed polypeptides with less than 100% identity to SEQ ID NO: 10 must be more highly expressed in normal lung tissue compared to lung tumor, or be encoded by a polynucleotide that is more highly expressed in normal lung tissue compared to lung tumor. It is well-known in the art that proteins related to the protein of interest can be used, for example, to generate antibodies to the protein of interest. As amended, the limited breadth of the claims combined with the functional limitation is sufficient to enable the claims.

In view of the above arguments and amendments, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejected Claims 1-13 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The PTO states that the claims do not require that the polypeptide possess any particular biological activity,. any particular conserved structure, or other disclosed distinguishing feature. The PTO also notes that PRO874 is less than a full length polypeptide because the amino acid sequence of SEQ ID NO: 10 does not begin with an initiator methionine.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to

artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The subject matter of the pending claims concerns polypeptides having a specified sequence identity with the disclosed polypeptide sequence of SEQ ID NO: 10, and as amended, with the functional recitation: "wherein said isolated polypeptide is more highly expressed in normal lung tissue compared to lung tumor, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal lung tissue compared to lung tumor". Applicants have also stated that amino acid 34 of SEQ ID NO: 10 is the initiator methionine, and that amino acids 1-33 are not part of PRO874. Thus, the full-length PRO874 polypeptide has been disclosed.

Based on the detailed description of the cloning and expression of PRO874 in the specification, the description of the gene amplification assay, the actual reduction to practice of sequences SEQ ID NOs: 9 and 10, and the functional recitation in the instant claims, Applicants

submit that one of skill in the art would know that Applicants possessed the subject matter of the pending claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-6, 8-10, 12 and 13 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the recitation of "signal peptide," and "the extracellular domain." The PTO also argues that the full-length polypeptide has not been disclosed so it is not know if the entire extracellular domain is disclosed.

As indicated above, the full-length PRO874 polypeptide is amino acids 34-321 of SEQ ID NO: 10. Applicants have amended the claims to eliminate any recitation of a signal peptide, and have specified the amino acids of the extracellular domain. In light of these arguments and amendments, Applicants request that the PTO withdraw the indefiniteness rejections under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §102(b) – Anticipation

The PTO rejects Claims 1-13 as anticipated under 35 U.S.C. § 102(b) by Baker (WO 99/63088 A2), based on an effective filing date of May 1, 2002, the filing date of the instant application. The PTO states that Baker discloses an isolated polypeptide that is identical to the amino acid sequence of SEQ ID NO: 10.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, with is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/12252 filed 6/2/1999 (the Baker reference), which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/088030 filed 6/4/1998.

Applicants submit that for the reasons stated above, the claimed polypeptides have a credible, substantial, and specific utility and are enabled. The sequences of SEQ ID NOs: 9 and

10 were first disclosed in US Provisional Application 60/088030 filed 6/4/1998. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Thus, the instant application is entitled to a priority date of 8/24/2000 at the latest.

The Baker reference, to which this application claims priority, was published on 12/9/1999, less than a year before the latest possible priority date of the instant application – 8/24/2000. Thus, Baker is not available as prior art under §102(b) against the instant application.

Applicants also note that to anticipate, the subject matter disclosed in Baker must be enabled. To the extent that Baker is enabled, then the instant application is likewise enabled, and the PTO must grant the instant application an effective filing date of when the Baker application was filed, 6/2/1999. This would also prohibit the use of the Baker application as prior art under §102(b).

In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the rejection under §102(b).

Rejection under 35 U.S.C. §103(a) – Obviousness

The PTO rejects Claims 1-4 and 12 under 35 U.S.C. § 103(a) as unpatentable over TrEMBL protein sequence database accession no. Q9Y332 in view of Sibson (WO 94/01548), based on an effective filing date of May 1, 2002, the filing date of the instant application. The PTO asserts that Q9Y332 discloses the translation of a coding sequence, which is 97.5% identical to SEQ ID NO: 10. The PTO states that TrEMBL dose not disclose an isolated protein. However, the PTO argues that it would have been obvious to one of skill in the art to express and isolate the encoded protein. The PTO concludes that the invention is obvious in light of the prior art.

As discussed above, Applicants have claimed priority to U.S. Provisional Application No. 60/088030 filed on June 4, 1998. This application includes the disclosure of the full length sequence of SEQ ID NOS: 9 and 10. As the June 4, 1998 date precedes the date of Q9Y332, November 1, 1999, Applicants have shown possession of the claimed invention prior to publication of Q9Y332.

The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention".

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical

compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority back to a disclosure that predates the cited references. Q9Y332 discloses a polypeptide sequence that is 97.5% identical to SEQ ID NO: 10, and nothing more. Applicants have demonstrated, by means of the disclosure in their provisional application filed June 4, 1998, that they were in possession of so much of the claimed invention, i.e. SEQ ID NO: 10, as is disclosed in the Q9Y332 reference dated November 1, 1999. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 USC §103 be withdrawn.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Dec. 7, 2004

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